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CHRONIC KIDNEY DISEASE. NUTRITION, INFLAMMATION AND OXIDATIVE STRESS

SP397 FETUIN-A ATTENUATES MINERAL NANOPARTICLE ACTIVATION OF THE NLRP3 INFLAMMASOME IN THE HUMAN MACROPHAGE

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Introduction and Aims: Mineral nanoparticles may directly link inflammatory and calcification processes that often co-exist in patients with CKD and in other age-related vascular diseases. Synthetic mineral nanoparticles are strong activators of a pro-inflammatory response in the macrophage *in vitro*, inducing interleukin (IL)-1β secretion via activation of the NOD-like receptor protein-3 (NLRP3) inflammasome. However, serum-derived mineral nanoparticles, colloidal complexes of insoluble mineral and mineral-binding proteins, so-called calciprotein particles (CPP), appear comparatively benign. This implies that mineral-binding proteins such as fetuin-A, abundant in extracellular fluid and major constituents of native CPP, may regulate the inflammatory potential of mineral nanoparticles and may thus be a key determinant of cellular toxicity.
Methods: We studied the ability of amorphous (CPP-I) and crystalline (CPP-II) serum-derived mineral nanoparticles to prime and activate the NLRP3 inflammasome in human macrophage derived from peripheral monocytes, and compared this to the effect of synthetic hydroxyapatite nanocrystals and other known particulate/soluble inducers of the inflammasome platform.
Results: Although CPP-I were rapidly internalised via class A scavenger receptor-(SR-A)-mediated endocytosis, they failed to prime or activate the inflammasome even at high levels. In contrast, exposure of naïve cells to CPP-II, primed inflammatory cytokine synthesis through Toll-like receptor (TLR)-mediated/NF-κB-dependent signalling. Priming was potentiated by immunochemical blockade of the SR-A. Endocytosis of CPP-II resulted in activation of the NLRP3 inflammasome at very high levels through elevations in intracellular reactive oxygen species, calcium and cathepsin B release, secondary to endolysosomal destabilisation. Equivalent loads of synthetic hydroxyapatite nanocrystals induced greater release of IL-1β from macrophage, portending to a protective role for mineral-binding proteins in this context. Importantly, fetuin-A was found to inhibit cathepsin B activity and hence reveals one pathway through which this mineral-binding protein might limit activation of intracellular danger sensors and unwanted inflammatory reactions in response to physiologic mineral debris. Moreover, that CPP-II only activated the inflammasome at levels far exceeding than those detected in human serum suggests that such endogenous particulates are unlikely to be potently pro-inflammatory.
Conclusions: Fetuin-A limits mineral nanoparticle activation of the NLRP3 inflammasome. Further work is needed to substantiate the involvement of native serum-derived mineral nanoparticles in the pathogenesis of inflammatory vascular disease *in vivo*.